ANTIMICROBIAL RESISTANCE PATTERN OF BACTERIAL ISOLATES COMMUNITY ACQUIRED PNEUMONIA (CAP): EPIDEMIOLOGY, PATHOPHYSIOLOGY AND DIAGNOSIS

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Article History: Received: 13.05.2023 **Revised:**04.06.2023 **Accepted:** 27.06.2023

Abstract:

Despite improvements in the clinical management of patients with community-acquired pneumonia (CAP) over the last decade, the incidence of the condition remains high, especially in Europe. Globally, pneumonia continues to be associated with high morbidity, mortality, and health costs. Moreover, its management poses many challenges. The microbial identification of pathogens remains difficult even though new molecular tests have been developed, mainly because of the difficulties interpreting the results. Also, the epidemiological changes due to serotype replacement after introducing the pneumococcal conjugate vaccine represent an emerging issue. Whereas the lungs were once thought to be sterile, it is now known that there is a respiratory microbiome with a dynamic microbiological ecosystem. However, this is a relatively unknown field. This review article provides an overview of our current understanding of the epidemiology, physiopathology, and diagnosis of pneumonia.

Keywords: Epidemiology; community-acquired pneumonia (CAP); pneumonia.

DOI: - 10.53555/ecb/2023.12.1083

Introduction:

Throughout human history Pneumonia has been a common disease the word "pneumonia" originates from the ancient Greek word "pneumon," which means "lung," so the word "pneumonia" becomes "lung disease. **(1)**

Hippocrates referred to pneumonia as a disease "named by the ancients". Maimonides (1135–1204 AD) observed the basic symptoms that occur in pneumonia; acute fever, sticking pleurisy pain in the side, short rapid breaths, serrated pulse and cough." This clinical description is similar to those found in modern textbooks, and it reflected the extent of medical knowledge through the middle Ages into the 19th century. **(2).**

Edwin Klebs was the first to observe bacteria in the airways of persons having died of pneumonia in 1875**. (3).**

Carl Friedländer and Albert Fraenkel in 1882 and 1884 identified the two common

bacterial causes, Streptococcus pneumoniae and Klebsiella pneumonia. **(4)**

Sir William Osler, known as "the father of modern medicine", appreciated the death and disability caused by pneumonia, describing it as the "captain of the men of death" in 1918. Osler also described pneumonia as "the old man's friend" as death was often quick and painless when there were much slower and more painful ways to die. **(5).**

Epidemiology:-

World Health Organization (WHO) reported that Pneumonia is the single largest infectious cause of death in children worldwide. It accounts for 14% of all deaths of children under 5 years old, killing 740 180 children in 2019 **(6)**

According to the United Nations Children's Fund (UNICEF), every day, at least one child dies every 45 seconds from pneumonia. Almost all of these deaths are preventable **(7).**

The annual incidence of pneumonia requiring hospitalization was found in one study to be 15.7 cases per 10,000 children and higher among children under 2 years of age **(8)** .

Pathophysiology:-

Pneumonia develops when the normal defense mechanism in the lower respiratory tract are disrupted, and overwhelmed by viruses or bacteria in the lower airways. **(9).**

The normal defense mechanisms are disrupted most commonly by respiratory viral infections, but also by chemical irritants and environmental pollutants. Proliferation of bacteria in alveoli triggers an immune and inflammatory response.

As a result, there is alveolar congestion, WBC infiltration, alveolar edema, and deposition of cellular debris in the alveoli. This decreases lung compliance, collapse of alveoli and lung ventilation-perfusion mismatch giving rise to the signs and symptoms of CAP**. (10)**

Risk factors:-

While most healthy children can fight the infection with their natural defenses, research had been conducted to identify the risk factors of pneumonia. **(11).**

Definite risk factors

Malnutrition Crowding Indoor air pollution. Non-exclusive breastfeeding "during the first 4 months of life" - Low birth weight "≤ 2500 g" Lack of measles immunization "within the first 12 months of life"

Likely risk factors

Parental smoking Zinc deficiency - Vitamin A deficiency Concomitant diseases e.g. diarrhea, heart disease, asthma. **(12).**

Pathology:-

<u>Consolidation</u>:

- Congestion usually occurs within the first 24 hours of pneumonia.
- Cellular exudates containing neutrophils ,lymphocytes and fibrin replaces the alveolar air
- Capillaries in the surrounding alveolar walls become congested
- The infections spreads to the hilum and pleura fairly rapidly
- Pleurisy occurs

- Marked by coughing and deep breathing **(13).**

Red hepatization:

- Occurs in the 2-3 days after consolidation
- At this point the consistency of the lungs resembles that of the liver
- The lungs become hyperemic
- Alveolar capillaries are engorged with blood
- Fibrous exudate fill the alveoli
- This stage is "characterized " by the presence of many erythrocytes, neutrophils, desquamated epithelial cells and fibrin within the alveoli

Gray hepatization:

- Occurs in the last 2-3 days after Red Hepatization
- This is an a vascular stage
- The lung appears grey brown to yellow because of fibrino-purulant exudates , disintegration of red cells and hemosiderin
- The pressure of the exudates in the alveoli causes compression of the capillaries.
- Leukocytes migrate into the congested alveoli.

Resolution:

- This stage is characterized by the resorption and restoration of the pulmonary architecture.
- A large number of macrophages enter the alveolar spaces
- Phagocytosis of the bacteria laden leucocytes occurs
- Consolidation tissue re-aerates and the fluid infiltrate causes sputum
- Fibrinous inflammation may extend to and cross the pleural space, causing a rub heard by auscultation and it may lead to resolution or to organization and pleural adhesions. **(14).**

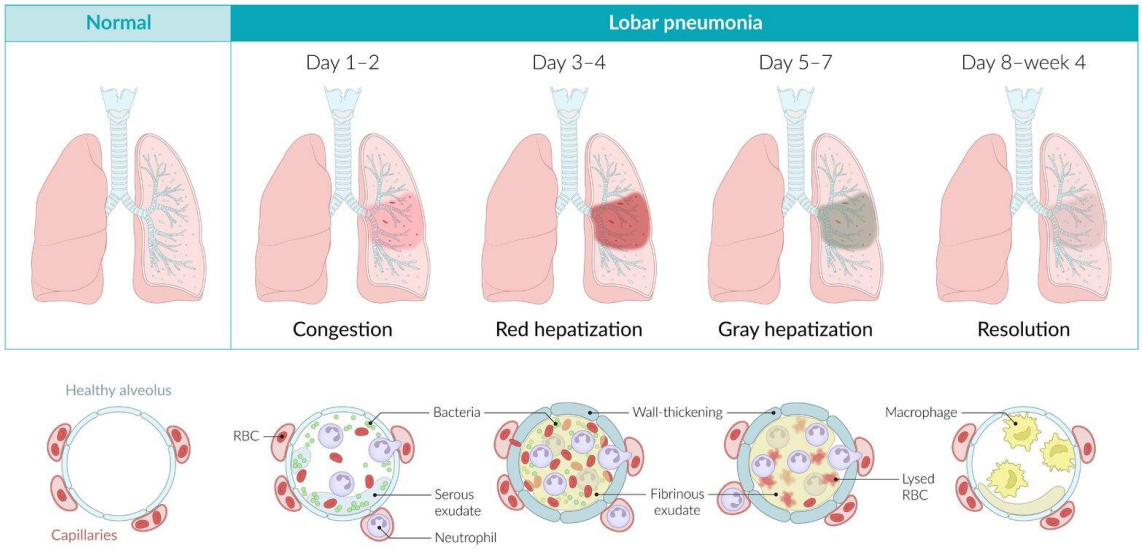


Figure (1) the four phases of Pneumonia ***(14)***

Classification:-

A. Anatomical: Lobar, bronchopneumonia or interstitial pneumonia

B. Etiological: infectious or noninfectious.

Bronchopneumonia

Inflammation is centered in the bronchioles and leads to the production of a mucopurulant exudate that obstructs some of these small airways and causes patchy consolidation of the adjacent lobules

Lobar pneumonia

"Typical " pneumonia that localized to one or more lobes of the lung in which the affected lobe or lobes are completely consolidated

→ Multi lobar pneumonia refers to the involvement of multiple lobes in a single lung or both lungs.

→ Pan lobar pneumonia involves all the lobes of a single lung. **(15)**

Interstitial pneumonitis

Refers to inflammation of the interstitium, which is composed of the walls of the alveoli, the alveolar sacs and ducts, and the bronchioles.

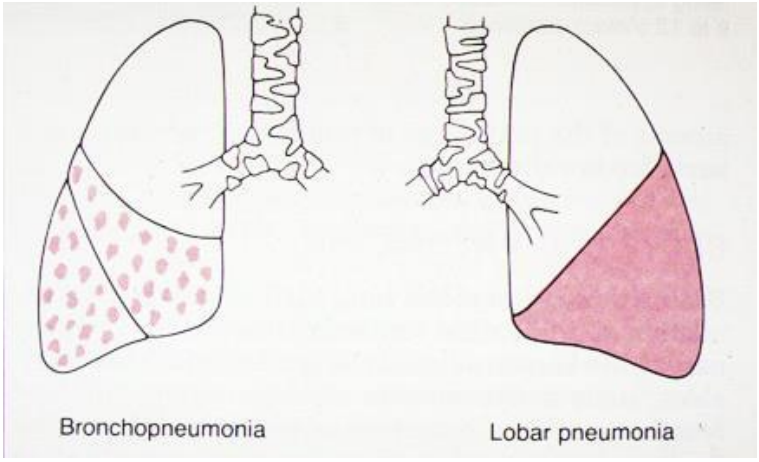


*Figure (2) a comparison of bronchopneumonia and lobar pneumonia **(15)**.*

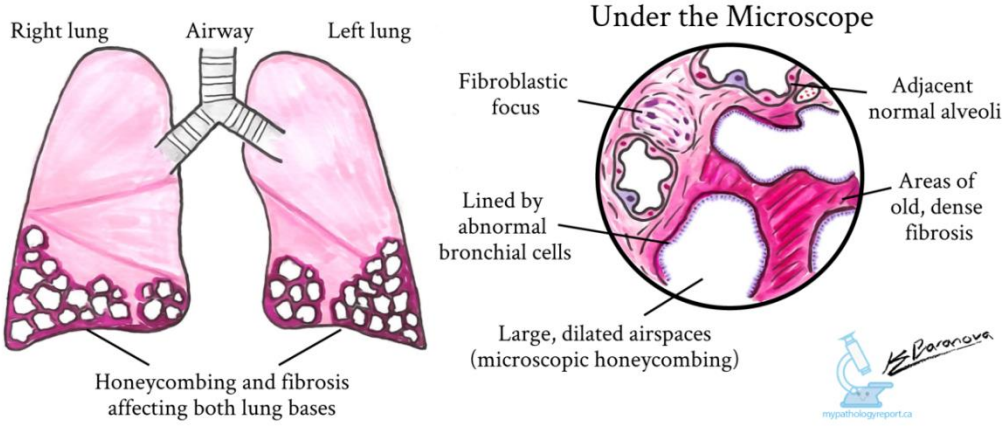


Figure (3) interstitial pneumonia

Infective pneumonia

It is caused by bacterial, viral, or fungal infections. Common causative organisms include Streptococcus pneumonia, Homophiles influenza, and viruses like influenza virus. Antibiotics are typically used to treat infective pneumonia. **(16)**

Non-infective pneumonia

Has other causes besides infections, like chemical/aspiration pneumonia from inhaling vomit or stomach acid, radiation pneumonia from exposure to radiation, and pneumonia caused By certain drugs or autoimmune disorders. **(17)**

Etiology:-

Etiology of pneumonia can be classified according to immunity state; in immune - compromised and immune-competent patients, the etiology of CAP varies by age as viral organisms predominating in younger children and bacterial causes increasing with age .**(18)**

Children who are immune-compromised, whether secondary to HIV infection/AIDS, an immune disorder, or chemotherapy for a malignancy, are at risk for pneumonias caused by opportunistic agents virtually any bacteria, virus, fungus, or even parasite can invade and infect the lungs if the immune system is sufficiently impaired.

Common Pathogens by age

Table 1:Bacterial pneumonia etiology **according to age (19).**

Age	**Bacteria**
Newborn	Group B Streptococcus Escherichia coli Klebsiella pneumoniae Listeria monocytogenes Proteus
1–3 months	Chlamydia trachomatis Group B Streptococcus Staphylococcus aureus Haemophilus influenzae Streptococcus pneumoniae
3 months to 5 years old	Streptococcus pneumoniae Homophiles influenza Staphylococcus aureus Mycoplasma pneumonia
Older than 5 years old	Streptococcus pneumonia Mycoplasma pneumoniae Staphylococcus aureus

	homophiles influenza Moraxella catarrhalis Legionella pneumonia

Table 2; **viral pneumonia etiology according to age (18).**

Age	Virus
Newborn	Herpes simplex virus Respiratory syncytial virus Human Rhinovirus Adenovirus Influenza A, B Coronavirus Para influenza 1, 2, 3
1–3 months1–3 months	Respiratory syncytial virus Human Rhinovirus Adenovirus Influenza A, B Coronavirus Para influenza 1, 2, 3
3 months to 5 years old	Respiratory syncytial virus Human Rhinovirus Human metapneumovirus Adenovirus Influenza A, B Para influenza 1, 2, 3 Coronavirus
Older than 5 years old	Human rhinovirus Influenza A, B Respiratory syncytial virus Human metapneumovirus Parainfluenza 1, 2, 3 Coronavirus Adenovirus

Diagnosis:-

Pneumonia is a clinical diagnosis based on clinical evidence and radiographic findings, not laboratory evidence. Consider microbiological studies and advanced diagnostics based on patient history, comorbidities, severity, and entity of pneumonia. **(20).**

However, lab studies can be used to support or refute the clinical assessment of severity and follow up. **(21).**

- **Clinical diagnosis**
  - ♦ WHO uses tachypnea and retractions to diagnose pneumonia in children ≤5 years old .
  - ♦ Tachypnea becomes less sensitive and specific as age increase **(18).**

Symptoms

General

→ Typical pneumonia is characterized by a sudden onset of symptoms caused by lobar infiltration

→ Severe malaise

→ Gastro-intestinal symptoms e.g. anorexia , vomiting
→ High persistent fever **(9)**

Local

→ Productive cough with purulent sputum (yellow-greenish)
→ Crackles and bronchial breath sounds on auscultation
→ Decreased breath sounds
→ Enhanced bronchophony ,ego phony, and tactile fremitus
→ Dullness on percussion
→ Tachypnea and dyspnea
→ (nasal flaring, thoracic retractions)
→ Pleuritic chest pain
→ when breathing, often accompanying
→ Pain that radiates to the abdomen and epigastric region (particularly in children; see also "Pneumonia in children")

If there is discrepancy between general symptoms it may a strong indication to atypical pneumonia **(9).**

Signs

General

- Lethargy/ un well appearance
- Signs of RDS
- Apnea
- chest in drawing
- Hypoxemia ↓92% on room air
- Tachypnea for age **(22).**

Age	Approximate normal respiratory rates (breaths/min)	Upper limit that should be used to define tachypnea (breaths/min)
<2 months	34–50	60
2–12 months	25–40	50
1–5 years	20–30	40
>5 years	15–25	30

Adapted from reference 14

Local

→ Crackles and bronchial breath sounds on auscultation
→ Decreased breath sounds
→ Enhanced bronchophony ,egophony, and tactile fremitus
→ Dullness on percussion
→ Tachypnea and dyspnea by inspection
→ (nasal flaring
→ Grunting
→ Thoracic retractions (subcostal , intercostal , suprasternal)

Lack of wheezing is an indicator of Mycoplasma pneumoniae in children with pneumonia, but as an indicator it is not accurate enough to decide whether or not macrolide treatment should be used. The presence of chest pain in children with pneumonia doubles the probability of Mycoplasma pneumonia**. (22).**

CAP severity assessment

The World Health Organization (WHO) defines "pneumonia" in children as presence of cough or difficulty breathing associated with fast breathing or chest in drawing in children 2–59 months of age, whereas "severe pneumonia" is defined as pneumonia plus inability to drink, persistent

vomiting, convulsions, lethargy, stridor, or severe malnutrition .These criteria were developed for use in countries with limited resources, and they are highly sensitive at the cost of specificity **(23).**

Assess the likelihood and severity of CAP by

- ♦ Fever
- ♦ Tachypnea
- ♦ Cough
- ♦ Breathlessness
- ♦ Chest wall recession
- ♦ Chest pain

Respiratory rate and dyspnea are useful measures of severity and predict oxygen requirement **(24).**

Level of distress	Description of patient	O_2 saturation	PEFR predicted	CTAS level
Severe	Fatiguing from excessive work of breathing, cyanosis, single-word speech, unable to speak, upper airway obstruction, lethargic or confused	<90%	—	I
Moderate	Increased work of breathing, speaking phrases or clipped sentences, significant or worsening stridor but airway protected	<92%	<40% predicted	II
Mild / moderate	Dyspnea, tachypnea, shortness of breath on exertion, no obvious increased work of breathing, able to speak in sentences, stridor without any obvious airway obstruction	92% to 94%	40% to 60% predicted	III

PEFR = peak expiratory flow rate.

Laboratory studies

Routine

- ♦ **Complete blood count (CBC),**

Complete blood counts are not routinely recommended in the evaluation of pneumonia in either the outpatient or inpatient settings, as white blood cell count is rarely useful to differentiate bacterial from viral infection or to prognosticate children with CAP. (**18).**

- WBC <15,000/μL suggests a nonbacterial etiology. However, neutropenic and severely ill patients may have low WBC.
- WBC >15,000/μL is suggestive of bacterial disease. However, children with M. pneumonia, influenza, or adenovirus may have WBC >15,000/μL. **(25).**

Peripheral eosinophilia in infants with a febrile pneumonia of young infants is suggestive of Chlamydia trachomatis. **(26).**

- ♦ **Acute phase reactants:**
- ✓ Erythrocyte sedimentation rate (ESR),

- ✓ C-reactive protein (CRP),
- ✓ Pro calcitonin (PCT)

↑ CRP, ↑ ESR, leukocytosis ; should not be used to diagnose CAP but used for severity and follow up. **(27)**

- **Serum pro calcitonin (PCT):**

PCT can be used to guide antibiotic treatment but should not be used to decide if antibiotic therapy is necessary on its own. **(28).**

PCT levels ≥ 0.25 mcg/L correlate with an increased probability of a bacterial infection.

Low PCT level after 2–3 days of antibiotic therapy can facilitate the decision to discontinue antibiotics**. (29).**

Decrease of PCT to ≤ 80% of peak level

Decrease of PCT to < 0.25 mcg/L (**28).**

- **ABG**: ↓ PaO2 : Indicated in patients with dyspnea or if SpO2 < 94%in room air **(30)**
- **Basal metabolic rate (BMP**), **liver function tests (LFT**): To evaluate for sepsis and end-organ damage. Legionella pneumonia can also cause LFT abnormalities.

Microbiological studies

Blood Culture

Blood cultures are not routinely recommended in otherwise healthy, immunized children with mild CAP and planned outpatient treatment due to their very low yield (< 2%, less than the typically reported blood culture contamination rate)**(31).**

Blood cultures are recommended for all children hospitalized with presumed bacterial CAP**. (32).**

Blood cultures are positive in less than 3% of children hospitalized with CAP, but higher (~20%) in children with Para pneumonic effusion/empyema**. (33).**

Sputum Gram Stain and Culture

Gram stain and culture of expectorated sputum should be attempted in children with severe disease, failure of outpatient therapy, and intensive care unit admission. **(34)**

Sputum is rarely produced in children younger than 10 years of age, and samples are always contaminated by oral flora. In the cooperative older child with a productive cough, a sputum Gram stain may be obtained **(35)**

Testing for viral pathogens

Rapid respiratory viral testing (RSV and Inf A & B), direct fluorescent antibody testing or by the more sensitive polymerase chain reaction (PCR) is recommended for all children hospitalized with CAP. **(18)**

Imaging

A. Chest x-ray (poster anterior and lateral view)

Chest radiography has long been considered the reference standard for the diagnosis of pneumonia in high resource settings.

Despite the reliance on chest radiography, it is neither 100% sensitive nor 100% specific; however, one study found that a negative chest radiograph has a negative predictive value of 98.8%; therefore a negative chest radiograph excludes pneumonia in the majority of children**. (36).**

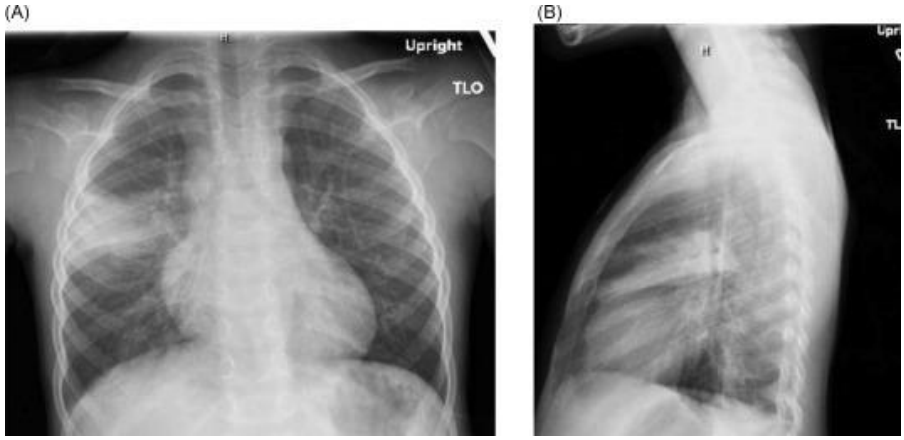
- X-ray findings

→ Lobar pneumonia: Opacity of one or more pulmonary lobes

→Bronchopneumonia: Poorly defined patchy infiltrates scattered throughout the lungs.

→Atypical or interstitial pneumonia: Diffuse reticular opacity, absent (or minimal) consolidation.

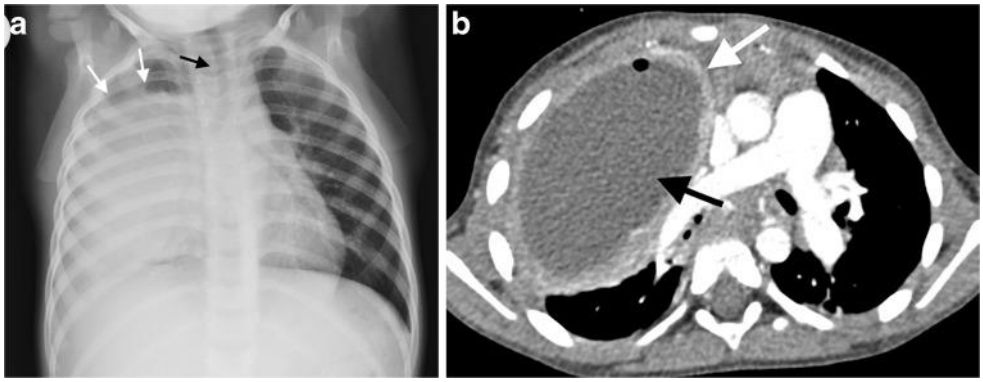
Significant hilar adenopathy may suggest fungi, M. pneumonia or M. tuberculosis. Nodular infiltrates may be seen with Pneumocystis jiroveci, fungi, viruses and atypical bacteria. Pneumatoceles are frequently detected in children with pneumonia secondary to S. aurous. **(37).**



(A and B) PA and lateral chest radiograph demonstrating a right middle lobe consolidation consistent with pneumonia **(18).**

B. Chest computed tomography (CT)

Should be considered in situations where potentially severe findings on chest radiography, such as nodular infiltrates, abscesses, necrotizing pneumonia or moderate-to-large effusions, need to be further delineated. **(38).**



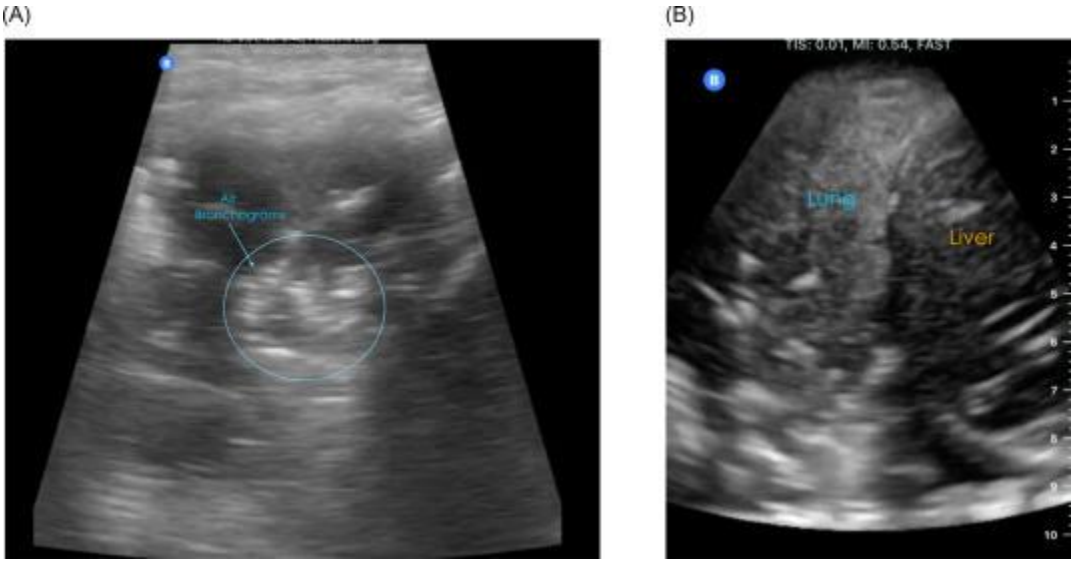
Lung abscess in a 2-year-old boy who failed to respond to antibiotic treatment for pneumonia. **A** Chest radiograph demonstrates an expansible dense opacity in the right lung with outwardly convex superior margin (*white arrows*) and mass effect on the mediastinum (*black arrow*). **B** Axial contrast-enhanced CT demonstrates a large abscess (*black arrow*) in the right lung with a well-defined, thick wall that shows some enhancement (*white arrow*) and displacement of the mediastinum to the left. **(39)**

C. Lung ultrasound in pneumonia (US)

High sensitive and specific for the diagnosis of pneumonia. **(40).**

- **Indications**

1. Evaluation of suspected pneumonia
2. Assessment of undifferentiated dyspnea



(A and B). (A) Air bronchograms on lung ultrasound demonstrating consolidative pneumonia, (B) hepatization of the lung typical of consolidative pneumonia on ultrasound. **(18)**

Follow-Up Imaging

Routine follow-up chest radiographs are not recommended in children who improve with outpatient or inpatient management**(41).**

Repeat chest radiographs are recommended in children who do not improve or deteriorate within 48–72 h of antibiotic therapy or in patients with complicated pneumonia with worsening respiratory distress. Patients with recurrent pneumonia involving the same lobe or those with lobar collapse at diagnosis should have repeated films in 4–6 weeks to evaluate for possible underlying predisposition to lobar collapse such as anatomic anomaly, chest mass or foreign body aspiration. **(41).**

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